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By Michelle Chan
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PATENT
100/00343

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

J. WALLACE PARCE

Application No.: To be Assigned

Filed: Herewith

For: HIGH THROUGHPUT SCREENING ASSAY SYSTEMS IN MICROSCALE FLUIDIC DEVICES

Examiner: To be Assigned

Art Unit:

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination on the merits, Applicants respectfully request entry and consideration of the following remarks. Please note that this preliminary amendment copies claims 1-8, 9-10, 13-17 and 19-22 from U.S. Patent No. 6,171,865, issued January 9, 2001 to Weigl et al. The following documents are submitted herewith:

1. a courtesy copy of U.S. Patent No. 6,171,865 for the Examiner's convenience;

2. a continuation application with declaration; and

3. an IDS with 1449 forms citing references form parent applications USSN 09/346,660 filed July 1, 1999 and USSN 08/671,987 (now U.S. Patent 5,942,443) filed June 28, 1996.

4. Table 1 providing support for copied claims.

IN THE SPECIFICATION:

Please insert the following priority information beginning on page 1, line 7:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 09/346,660, filed July 1, 1999, which is a continuation of U.S. Patent Application No. 08/671,987, filed June 28, 1996 (now U.S. Pat. 5,942,443). This application also claims the benefit of U.S. Patent Application No. 09/664,847, filed September 19, 2000, which is a continuation of U.S. Patent Application No. 09/179,242, filed October 26, 1998 (now U.S. Pat. 6,156,181), which is a continuation of U.S. Patent Application No. 08/843,212, filed April 14, 1997 (now U.S. Pat. 5,885,470), which claims the benefit of U.S. Provisional Patent Application No. 60/015,498.

IN THE CLAIMS:

Please cancel claims 1-74 without prejudice.

Please add the following NEW claims:

75. A device for detecting the presence or determining the concentration of analyte particles in a sample stream comprising:

a) a laminar flow channel;

b) at least three inlet means in fluid connection with said laminar flow channel for respectively conducting into said laminar flow channel (1) an indicator stream, (2) a sample stream, and (3) a reference stream; and

c) wherein said laminar flow channel has a dimension sufficiently small to allow laminar flow of said streams adjacent to each other and a length sufficient to allow analyte particles to diffuse from at least one stream selected from the group consisting of said sample stream and said reference stream into the indicator stream to form at least one detection area.

76. A device of claim 75 also comprising outlet means comprising branching channels for separation of the streams into one or more channels.

77. The device of claim 76 wherein said outlet means comprise smaller channels for conducting the sample stream than for conducting the indicator stream.

78. A device of claim 75 further comprising detecting means positioned relative to said flow channel such that said detecting means can detect a change in a detectable property in at least one of said streams.

79. A device of claim 78 wherein said detecting means comprise components selected from the group consisting of a charge coupled device camera, a diode array detector, a fluorescence detector, and an electrochemical detector.

80. A device of claim 75 further comprising inlet means for conducting at least one additional reference or sample stream in laminar flow contact with said indicator stream.

81. A device of claim 75 further comprising means for dividing said indicator or sample stream into at least two separate streams and conducting said separate streams into said laminar flow channel.

82. A device of claim 75 further comprising a plurality of laminar flow channels in fluid communication with an indicator stream channel and means for conducting portions of an indicator stream from said indicator stream channel into laminar flow with separate sample or reference streams in said laminar flow channels.

83. A method for detecting the presence or determining the concentration of analyte particles in a sample stream, comprising:

a) conducting said sample stream into a laminar flow channel;

b) conducting an indicator stream, said indicator stream comprising an indicator substance which indicates the presence of said analyte particles by a change in a detectable property when contacted with particles of said analyte, into said laminar flow channel, whereby said sample stream and said indicator stream flow in adjacent laminar flow in said channel;

c) conducting a reference stream, comprising a constant concentration of 0 or greater of reference particles into said laminar flow channel, whereby said reference stream flows in a laminar stream adjacent to said indicator stream;

d) allowing analyte particles to diffuse into said indicator stream;

e) allowing reference particles to diffuse into said indicator stream;

f) detecting the presence or determining the concentration of said analyte and reference particles in said indicator stream; and

g) separately conducting at least one of said streams out of said laminar flow channel.

84. The method of claim 83, wherein the reference stream contains a concentration of analyte particles which is greater than zero.

85. The method of claim 83, wherein two reference streams are conducted into said laminar flow channel in adjacent laminar flow to said indicator stream.

86. A method of claim 83, wherein said reference stream is a control stream.

87. A method of claim 83, wherein said reference stream is an internal standard stream.

88. A method of claim 87, wherein said internal standard stream contains reference particles different from said analyte particles.

89. A method of claim 87, wherein said internal standard stream contains reference particles the same as said analyte particles.

90. A method of claim 83, wherein said reference stream is used as a calibration stream.

91. A method of claim 83 wherein the detectable property is selected from the group consisting of absorbance, chemiluminescence and fluorescence.

92. A method of claim 83, wherein the indicator substance is immobilized on a particulate substance carried within the indicator stream.

93. The method of claim 83 wherein step (g) comprises conducting the sample stream from said indicator stream.

REMARKS

With this amendment, claims 75-93 are pending in the application. New claims 75-93 are copied from claims 1-8, 9-10, 13-17 and 19-22 of U.S. Patent No. 6,171,865 with minor modifications. No new matter is being introduced by virtue of the new claims presented herewith. The claims and dependencies are renumbered to conform to claim numbering in the present case and to the claims which are presented.

Support for the new claims can be found throughout the specification. Table 1 below, sets forth claims from the '865 patent and the present claims along with example support for each claim limitation as found in the present specification.

Therefore, the new claims are supported by the specification and no new matter is added by virtue of the new claims. Applicants respectfully request that the claims be entered.

Respectfully submitted,

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	U.S. Patent No. 6,171,865	Present Application
Claim 1 of '865 patent. Claim 75 in present application.	1. A device for detecting the presence or determining the concentration of analyte particles in a sample stream comprising:	The present invention generally provides microfluidic devices for performing screening assays. For example, page 7, lines 3-9 generally describes microfluidic devices for screening compounds.
	a) a laminar flow channel;	Figure 1, element 110 illustrates a laminar flow channel on microfluidic device 102. See accompanying text on page 14, lines 27-30.
	b) at least three inlet means in fluid connection with said laminar flow channel for respectively conducting into said laminar flow channel (1) an indicator stream, (2) a sample stream, and (3) a reference stream; and	Figure 2A, illustrates three inlet means, 104, 112 and 106 in fluid connection with a laminar flow channel 110 for conducting into the channel, an indicator stream such as a fluorogenic substrate, a sample stream for e.g., an enzyme stream and a reference stream, for e.g., a control compound with no effect on the enzyme/substrate complex, see accompanying text on page 23, line 19 through page 24, line 4.
	c) wherein said laminar flow channel has a dimension sufficiently small to allow laminar flow of said streams adjacent to each other and a length sufficient to allow analyte particles to diffuse from at least one stream selected from the group consisting of said sample stream and said reference stream into the indicator stream to form at least one detection area.	Page 14, lines 27-35 describe channels having cross sectional dimensions in the range of 0.1µm to about 500µm. Therefore, the cross section of at least one channel will result in laminar flow of fluids within that channel. Example of this flow is described on page 23, line 19 through page 24, line 4 wherein a fluorogenic substrate, an enzyme and a test compound stream are flowed in a laminar flow within a channel to allow for particles from the test compound stream to diffuse into the fluorogenic stream.
Claim 2 of '865 patent. Claim 76 in present application.	A device of claim 1/75 also comprising outlet means comprising branching channels for separation of the streams into one or more channels.	Figure 6A and page 33, lines 9 –26 describe a microfluidic device comprising branching channels for separation of the streams into one or more channels.
Claim 3 of '865 patent. Claim 77 in present application.	The device of claim 2/76 wherein said outlet means comprise smaller channels for conducting the sample stream than for conducting the indicator stream.	Page 34 lines 9-10 describes channels having varying geometries.
Claim 4 of '865 patent. Claim 78 in present application.	A device of claim 1/75 further comprising detecting means positioned relative to said flow channel such that said detecting means can detect a change in a detectable property in at least one of said streams.	A detection means is described on page 32 lines 23-25 and is illustrated in Figures 4E-4F. Also, Figure 6,element 662 illustrates a detection means positioned relative to a flow channel for detection of a change in a detectable property in at least one of the streams.

Claim 5 of '865 patent. Claim 79 in present application.	A device of claim 4/78 wherein said detecting means comprise components selected from the group consisting of a charge coupled device camera, a diode array detector, a fluorescence detector, and an electrochemical detector.	Page 17, lines 10-28 describes optical detection means such as fluorescence and electrochemical detectors.
Claim 6 of '865 patent. Claim 80 in present application.	A device of claim 1/75 further comprising inlet means for conducting at least one additional reference or sample stream in laminar flow contact with said indicator stream.	Figure 1, element 106, provides a source of at least one additional stream to flow through channel 112 which enters into laminar flow contact with indictor stream in channel 110.
Claim 7 of '865 patent. Claim 81 in present application.	A device of claim1/75 further comprising means for dividing said indicator or sample stream into at least two separate streams and conducting said separate streams into said laminar flow channel.	Means for conducting and/or dividing flow of indicator or sample stream into at least two separate streams is described through out the specification. For example, see page 33, line 30 through page 34, line 8 and page 34, lines 21-29.
Claim 8 of '865 patent. Claim 82 in present application.	A device of claim 1/75 further comprising a plurality of laminar flow channels in fluid communication with an indicator stream channel and means for conducting portions of an indicator stream from said indicator stream channel into laminar flow with separate sample or reference streams in said laminar flow channels.	Plurality of laminar flow channels connected to an indicator stream channel for conducting portion of the indicator stream into laminar flow with separate samples is illustrated in Figures 6A-C and described on pages 33, line 30 through page 34, line 8 and page 34, lines 21-29.
Claim 10 of '865 patent. Claim 83 in present application.	A method for detecting the presence or determining the concentration of analyte particles in a sample stream, comprising:	The present invention provides devices and methods for detecting the presence of analyte particles in a sample stream. See page 7, line 33 through page 8, line3.
	a) conducting said sample stream into a laminar flow channel;	Figure 5, element 512 and accompanying text on page 25, lines 35 –37 describes conducting a sample stream into a laminar flow channel.
	b) conducting an indicator stream, said indicator stream comprising an indicator substance which indicates the presence of said analyte particles by a change in a detectable property when contacted with particles of said analyte, into said laminar flow channel, whereby said sample stream and said indicator stream flow in adjacent laminar flow in said channel;	Figure 5, and text on page 26, lines 12-15 illustrate conducting an indicator stream such as a labeled ligand into the laminar flow channel whereby, the indicator stream and the sample stream flow in adjacent laminar flow in the channel 510b

	c) conducting a reference stream, comprising a constant concentration of 0 or greater of reference particles into said laminar flow channel, whereby said reference stream flows in a laminar stream adjacent to said indicator stream;	Figure 5, page 25 lines 37-37, page 26, lines 6-15 and page 8, lines 29-32 describe flowing a control the laminar flow channel such that the control and the indicator stream flow adjacently in a laminar flow.
	d) allowing analyte particles to diffuse into said indicator stream;	Page 26, lines 6-10 describes the mixing of analyte particles from test compound into the indicator stream.
	e) allowing reference particles to diffuse into said indicator stream;	Page 26, lines 11-20 describe the mixing of the reference particles to diffuse into the indicator tream.
	f) detecting the presence or determining the concentration of said analyte and reference particles in said indicator stream; and	Detection of the presence of an analyte is described on pages 24, lines 15-18, page 25, lines 8-15 and is illustrated in Figure 5 as a detection window on channel 524.
	g) separately conducting at least one of said streams out of said laminar flow channel.	Page 26, lines 32-38 describes separately conducting the sample stream out of a reaction channel which is the laminar flow channel.
Claim 11 of '865 patent. Claim 84 in present application.	The method of claim 10/83, wherein the reference stream contains a concentration of analyte particles which is greater than zero.	Figure 2B, element 152 illustrates flowing test compounds or control streams into channel 112. Page 8, lines 29-32 describes a control sample that is used as a reference. See page 8, lines 29-32. Also see page 24, line 37 through page 25 line 8 for the description of different types of reference compounds.
Claim 13 of '865 patent. Claim 85 in present application.	The method of claim 10/83, wherein two reference streams are conducted into said laminar flow channel in adjacent laminar flow to said indicator stream.	Figure 2B illustrates the serial introduction of two reference plug streams into laminar flow channel wherein they are directed to flow in laminar flow adjacent to an indicator stream. See page 26, lines 11-20.
Claim 14 of '865 patent. Claim 86 in present application.	A method of claim 10/83, wherein said reference stream is a control stream.	See Figure 2B, element 152. See also page 24, line 36 through page 25, line 8.
Claim 15 of '865 patent. Claim 87 in present application.	A method of claim 10/83, wherein said reference stream is an internal standard stream.	The methods of the present invention describe internal standards such as spacer fluids that are be used as a standard for a constant signal. See page 24, lines 27-37.
Claim 16 of '865 patent. Claim 88 in present application.	A method of claim 15/87, wherein said internal standard stream contains reference particles different from said analyte particles.	See page 24, line 30 through page 25, line 3 for a description of a internal standard containing reference particles.

Claim 17 of '865 patent. Claim 89 in present application.	A method of claim 15/87, wherein said internal standard stream contains reference particles the same as said analyte particles.	See page 24, line 30 through page 25, line 3 for a description of a internal standard containing reference particles.
Claim 19 of '865 patent. Claim 90 in present application.	A method of claim 10/83, wherein said reference stream is used as a calibration stream.	See page 24, line 30 through page 25, line 4 for a description of a reference stream used as a calibration.
Claim 20 of '865 patent. Claim 91 in present application.	A method of claim 10/83 wherein the detectable property is selected from the group consisting of absorbance, chemiluminescence and fluorescence.	Page 17, lines 12-21 describes detectable properties such as fluorescence and absorbance.
Claim 21 of '865 patent. Claim 92 in present application.	A method of claim 10/83, wherein the indicator substance is immobilized on a particulate substance carried within the indicator stream.	Page 29, lines 26-31 illustrates an indicator substance immobilized on a particulate substance for e.g., a bead.
Claim 22 of '865 patent. Claim 93 in present application.	The method of claim 10/83 wherein step (g) comprises conducting the sample stream from said indicator stream.	Figure 5 illustrates conducting the sample stream from said indicator stream by flowing the sample stream out of laminar flow channel 510 into transfer channel 526. See accompanying text on page 26, lines 32-38.